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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,387	01/14/2005	Reiner Luttmann	SARTORIUS-12	2344

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EXAMINER	
HOBBS, MICHAEL L	

ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
10/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,387	LUTTMANN ET AL.	
	Examiner	Art Unit	
	MICHAEL HOBBS	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/10/2009 has been entered.

2. Claims 1-20 are pending further examination upon the merits.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cornelissen et al. (CAB8-Compuer Application in Biotechnology, June 25-27, 2001) in views of Major et al. (*Biotechnology and Bioengineering*, vol. 34, pp 592-599, 1989) and Gruenberg et al. (US 2002/0138454 A1) and in further views of Lucido et al. (US 6,402,941) and Bartok et al. (US 6,599,735 B1).

7. Cornelissen teaches an integrated bioprocess for the production of recombinant proteins by cultivating Pichia Pastoris. For claim 1, Cornelissen discloses using a device that includes bioreactor that cultivates cells which is connected to an upstream feed receptacle or glycerol feed (Fig. 3) and to a downstream cross-filtration or micro filtration unit (Fig. 3, page 1 section 2 paragraph 5). The micro-filtration unit is has a retentate line connected to the bioreactor and a permeate line which connects to a product harvest vessel (Fig. 3). The process is monitored by various sensors which report back to a control unit (Fig. 4) where these sensors consist of pO_2 control, an off gas analysis and the use of an HPLC to determine glycerol level in the reactor (section

7 page 6 paragraph 2). Furthermore, this control is analyzer (Fig. 3) which is connected to an agitator control, but not to a pump. Also, Cornelissen does not teach a second harvest vessel connected directly to the bioreactor.

8. Major discloses a continuous fermenter for lactate production by *Lactobacillus delbreuckii* with partial cell recycle using a hollow-fiber ultra-filtration cartridge. For claim 1, Major discloses withdrawing a whole-cell culture from the fermenter by a peristaltic pump that is upstream of a waste receiver or second harvest vessel (Fig. 1; page 594 second paragraph). It would be obvious to one of ordinary skill in the art to employ the step of using a waste receiver as suggested by Major in order to remove whole cells from the reactor of Cornelissen. The suggestion for doing so at the time would have been in order to maintain a constant volume in the fermenter (page 594 first paragraph lines 7-9). Major is silent regarding the analyzer being connected to the pump.

9. Gruenberg discloses a method of optimizing a bioprocess involving complex nutrient mixtures where there are several upstream reservoirs supplying culture medium to a bioreactor. For claim 1, Gruenberg discloses the step where the product is harvested into a vessel where the control to the pump is connected to a process computer via a RS-232 connection (Fig. 1). While not specifying that the motor is connected to an analyzer, the control unit (Fig. 1) is connected to the process computer and would indicate changes within the bioreactor that would initiate the pump to withdraw product from the bioreactor. Therefore, it would have been obvious to one of ordinary skill in the art to employ the process computer controlled pump as suggested

by Gruenberg to withdraw whole cells from the fermenter of Cornelissen and Major with a reasonable expectation of success.

10. Both Cornelissen and Gruenberg disclose the step of having a sensor such as a dissolved oxygen sensor connected to an analyzer or control unit where, in the case of Gruenberg, the control unit is connected to and controls the motor on the pump (Fig. 1 of Gruenberg). Furthermore, Cornelissen and Gruenberg disclose sensors that measure the metabolites of the cell culture, which are indirect measures of the cell concentration; they do not disclose the step of actually measuring the cell concentration within the bioreactor. The combined references of Cornelissen, Major and Gruenberg are silent regarding a cell concentration measurement step.

11. Lucido discloses an apparatus for the biological treatment of environmental contaminants and waste where the cell concentration of the microorganisms is determined by the turbidity of the solution. For claim 1, Lucido discloses the step of using an optical density sensor (sensor 22) to detect the turbidity of the solution where a higher turbidity reading in the bioreactor indicates a higher viable cell concentration (col. 6 lines 30-33). Lucido demonstrates another method used to monitor the extent of cell cultivation within a bioreactor using optical detectors instead of the metabolite sensors of Cornelissen and Gruenberg. Furthermore, the combined references demonstrate a need to monitor and control the cultivation within a bioreactor where the control means range from the metabolite sensors of Cornelissen and Gruenberg, the volumetric control of Major to the optical sensor of Lucido. The three methods perform the same task of monitoring the conditions within the bioreactor. Furthermore, these represent a finite

number of methods for monitoring the conditions within the bioreactor and would have been known to one of ordinary skill in the art at the time of the invention. Therefore, following rationale E of *KSR*, 550 U.S. at ____, 82 USPQ2d at 1397, it would have been obvious to one of ordinary skill in the art to employ the step of using the optical sensor of Lucido within the control unit of Cornelissen, Major and Gruenberg with a reasonable expectation of success.

12. With regards to the step of using a second regulator for operating an upstream feed pump, Cornelissen discloses using a weigh control that receives a weight value, V_L, from a scale (Fig. 3) and compares this value with a reference value, V_{LW}, that is inputted into the weight control regulator (Fig. 3, page 3 section 4 paragraph 6). However, Cornelissen is silent regarding the step of having this regulator connected to a feed pump instead of a harvest pump. Major, Gruenberg and Lucido are silent regarding a second regulator controlling a feed pump.

13. Bartok discloses a continuous fermentation system that includes the step of using a fermentation vessel (vessel 1) and includes upstream vessels (vessels 2) that are used to store the nutrient solutions for the fermentation process. Further, the system includes two regulators or control systems (computer 7 and control unit 11) that monitor and steer the entire process. For claim 1, Bartok discloses using a control unit (unit 11) or second regulator that monitors the process parameters from a control system (system 17) and further operates upstream feed pumps (pumps 3) in order to modify or control the dilution rate or pH of the system. The control unit (unit 11) is also connected to a scale (scale 4) that weighs the fermentation vessel (Fig. 1; col. 4 lines

43-61). Therefore, it would be obvious for one of ordinary skill in the art to employ the method of using the controller to operate an upstream feed pump suggested by Bartok within Cornelissen, Major, Gruenberg and Lucido with the predictable result of controlling the weight within the fermentation vessel.

14. With regards to claim 2, Cornelissen is silent regarding *in situ* sterilization of the process. For claim 2, Major discloses the step of sterilizing the hollow-fiber tube using and associated tube work with a sodium hypochlorite solution before each fermentation run (page 594 paragraph 2 lines 1-3). This step of sterilizing the filter and tubes is being interpreted as an *in situ* sterilization. Furthermore, one of ordinary skill in the art would recognize the benefits of sterilizing the filter and tubes ahead of time and flushing the lines in the manner described above in order to prevent cross-contamination between the batches. Furthermore, the sterilization step of Major solves the problem of sterilizing the equipment used in the fermentation process without having to disassemble the entire apparatus between different fermentation runs. Therefore, following rationale A of *KSR*, 550, U.S. at ____, USPQ2d at 1396, it would have been obvious to one of ordinary skill in the art to employ the sterilization step as suggested by Major in order to sterilize and prepare the filter and bioreactor of Cornelissen for another run with predictable results.

15. However, Cornelissen and Major are silent regarding this process being controlled by a computer or controller.

16. Gruenberg discloses a process computer that controls the operation of the fermentation process, but does not mention using the processor to control the

sterilization process of the bioreactor. However, it would be obvious to one of ordinary skill in the art to modify the sterilization process of Cornelissen and Major with the process computer of Gruenberg in order to automate the sterilization process so that it may be conducted *in situ* with a reasonable expectation of success.

17. For claim 3, Cornelissen teaches the step where the **valuable product** is recombinant proteins (Abstract). For claim 4, Cornelissen does not specify that the process is conducted in a sequential and integrated manner, but does imply that the process steps happen in a specific sequence. Referring to Figure 1 of the OA, each phase of production leads to another phase which strongly implies that the production of recombinant DNA as taught by Cornelissen is sequential. Further, the automation of this process as shown in Figure 4 of Cornelissen shows that each part of the process is integrated or coupled and are part of the whole process (page 6 section 8 paragraph 1). Regarding the method of producing biotechnologically valuable products as in claim 5, Cornelissen teaches that the cells adapt to the medium and that the cells are propagated at a constant growth rate, μ, for the batch phase (page 3 sections 3 and 4, Fig. 2) and for claim 6 Cornelissen teaches the step of using an induction substance such as methanol during the production phase (page. 3 section 3 paragraph3) . For claim 7, Cornelissen teaches the step of using a flow diffusion analysis (FDA) to regulate a second feed receptacle (page 3 section 4, Fig. 3). With regards to claim 8, Cornelissen teaches that the product is harvested from the bioreactor by using a cross-flow filtration step (page 1 section 2 paragraph 5), but does not specify that the product is harvested cell-free. However, since the cross-flow filtration step filters out the

recombinant DNA produced within the bioreactor, it is an intrinsic property of the product that it would be cell-free.

18. With regards to claim 9, Cornelissen teaches that the cell harvesting and media refreshing phase happen in parallel, but does not specifically teach that the retentate is harvested and that this step is followed by a medium refreshing phase. For claim 9, Major discloses the step of harvesting the whole cell mass or retentate from the bioreactor as discussed above and further includes the step of controlling the dilution rate and recycle ration by two peristaltic pumps which is being interpreted as the medium replenishing step (page 594 paragraph 1 lines 12-16). It would be obvious to one of ordinary skill in the art to employ the step of refreshing the culture medium as suggested by Major in the cultivation process of Cornelissen. The suggestion for doing so at the time would have been in order to maintain a constant volume in the fermenter (page 594 first paragraph lines 7-9).

19. For claim 10, Cornelissen teaches the step of sending the retentate back into the bioreactor (Fig. 3) and sending the permeate from the filter to the product harvest vessel (Fig. 3).

20. Regarding claim 11, Cornelissen teaches the step where the yeast used to produce the **recombinant DNA** is Pichia pastoris (Abstract) and for claim 12, Cornelissen teaches the step where the inducing substance is methanol (page 3 section 4, Fig. 1 & Fig. 3). Regarding claims 13 and 14, Cornelissen teaches maintaining the methanol level at a constant level and that glycerol is fed to the bioreactor (page 3 sections 3 & 4, Fig. 3).

21. For claim 15, Cornelissen does not specify that the process is conducted in a continuous and integrated manner, but does imply that the process is continuous and integrated. Referring to Figure 1 of the OA, each phase of production leads to another phase which strongly implies that the production of recombinant DNA as taught by Cornelissen is continuous. Further, the automation of this process as shown in Figure 4 of Cornelissen shows that each part of the process is integrated or coupled with every step and device of the larger process (page 6 section 8 paragraph 1).

22. For claim 16, the fresh media refill and cell harvesting are carried out in parallel (page 3 section 4 paragraph 6).

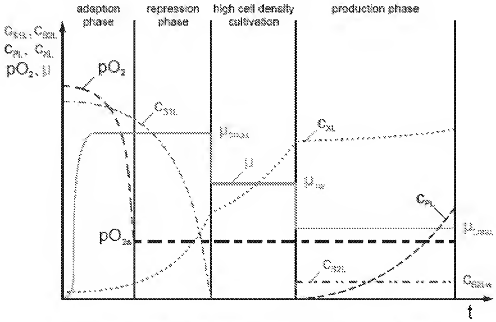

Fig. 2: Process course for automated production of recombinant proteins

Figure 1: Automated production of recombinant proteins (Cornelissen et al.)

23. Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cornelissen et al. (CAB8-Compuer Application in Biotechnology, June 25-27, 2001) in views of Major et al. (*Biotechnology and Bioengineering*, vol. 34, pp 592-599, 1989) and Gruenberg et al. (US 2002/0138454 A1) and in further view of and Bartok et al. (US 6,599,735 B1).

24. Cornelissen teaches an integrated bioprocess for the production of recombinant proteins by cultivating Pichia Pastoris. For claim 17, Cornelissen teaches a device that includes bioreactor that cultivates cells which is connected to an upstream feed receptacle or glycerol feed (Fig. 3) and to a downstream cross-filtration or micro filtration unit (Fig. 3, page 1 section 2 paragraph 5). The micro-filtration unit is has a retentate line connected to the bioreactor and a permeate line which connects to a product harvest vessel (Fig. 3). The process is monitored by various sensors which report back to a control unit (Fig. 4) where these sensors consist of pO_2 control, an off gas analysis and the use of an HPLC to determine glycerol level in the reactor (section 7 page 6 paragraph 2). Furthermore, this control is analyzer (Fig. 3) which is connected to an agitator control, but not to a pump. Also, Cornelissen does not teach a second harvest vessel connected directly to the bioreactor.

25. Major discloses a continuous fermenter for lactate production by *Lactobacillus delbreuckii* with partial cell recycle using a hollow-fiber ultra-filtration cartridge. For claim 17, Major discloses withdrawing a whole-cell culture from the fermenter by a peristaltic pump that is upstream of a waste receiver or second harvest vessel (Fig. 1; page 594 second paragraph). This would be obvious to one of ordinary skill in the art to

employ the waste receiver as suggested by Major in order to remove whole cells from the reactor of Cornelissen. The suggestion for doing so at the time would have been in order to maintain a constant volume in the fermenter (page 594 second paragraph). Major is silent regarding the analyzer being connected to the pump.

26. Gruenberg discloses a method of optimizing a bioprocess involving complex nutrient mixtures where there are several upstream reservoirs supplying culture medium to a bioreactor. For claim 17, Gruenberg discloses that the product is harvested into a vessel where the control to the pump is connected to a process computer via a RS-232 connection (Fig. 1). While not specifying that the motor is connected to an analyzer, the control unit (Fig. 1) is connected to the process computer and would indicate changes within the bioreactor that would initiate the pump to withdraw product from the bioreactor. Therefore, it would have been obvious to one of ordinary skill in the art to employ the process computer controlled pump as suggested by Gruenberg to withdraw whole cells from the fermenter of Cornelissen and Major with a reasonable expectation of success.

27. With regards to the second regulator for operating an upstream feed pump, Cornelissen discloses using a weigh control that receives a weight value, V_L, from a scale (Fig. 3) and compares this value with a reference value, V_{LW}, that is inputted into the weight control regulator (Fig. 3, page 3 section 4 paragraph 6). However, Cornelissen is silent regarding the regulator being connected to a feed pump instead of a harvest pump. Major and Gruenberg are silent regarding a second regulator controlling a feed pump.

28. Bartok discloses a continuous fermentation system that includes the step of using a fermentation vessel (vessel 1) and includes upstream vessels (vessels 2) that are used to store the nutrient solutions for the fermentation process. Further, the system includes two regulators or control systems (computer 7 and control unit 11) that monitor and steer the entire process. For claim 17, Bartok discloses using a control unit (unit 11) or second regulator that monitors the process parameters from a control system (system 17) and further operates upstream feed pumps (pumps 3) in order to modify or control the dilution rate or pH of the system. The control unit (unit 11) is also connected to a scale (scale 4) that weighs the fermentation vessel (Fig. 1; col. 4 lines 43-61). Therefore, it would be obvious for one of ordinary skill in the art to employ the controller to operate an upstream feed pump as suggested by Bartok within Cornelissen, Major, Gruenberg and Lucido with the predictable result of controlling the weight within the fermentation vessel.

29. For claim 18, Cornelissen further teaches that the concentration of methanol is controlled by a feed pump that is connected to a control device (Fig. 3, page 3 section 4 paragraph 5) and for claim 19 the control device is a flow diffusion analysis (FDA) system (Fig. 3). For claim 21, a weight control on the bioreactor is connected to a feed pump for the product harvest vessel (Fig. 3).

Response to Arguments

30. Applicant's arguments with respect to claims 1-19 have been considered but are moot in view of the new ground(s) of rejection.

31. The deficiencies within the previously applied references is corrected by the newly applied reference of Bartok which discloses a second controller or regulator that operates an upstream feed pump in response to the weight of a fermentation vessel.

32. Applicant argues that Cornelissen teaches away from using a reference value and regulator connected to a feed pump. While Cornelissen does not disclose this embodiment of the instant application, this deficiency within the reference is corrected by the applied references of both Gruenberg and Bartok which discloses feed pumps connected to a controller or process computer and where each of the supply vessels and bioreactors have a balance that is connected to the process computer. This demonstrates that the methods of having a controller operate either a feed pump or a harvest pump are alternative methods for controlling the weight within a bioreactor.

33. With regards to Applicant's argument regarding the applied reference of Lucido that the optical density sensor cannot be used with an automated system and that it is not analogous art, the Examiner respectfully disagrees. Lucido discloses the improvement of the instant claims of a sensor that can determine cell concentration within a culture vessel or bioreactor. Further, Lucido demonstrates that an optical density sensor to determine cell concentration would have been known to the skilled artisan at the time of the invention. Further, while Lucido is not drawn to a bioreactor for culturing *P. pastoris*, the culturing steps used within Lucido can be applied to *P. pastoris*. Also, while the system of Lucido is not automated, but providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art. See also MPEP 2144.04 II.

34. In response to applicant's argument starting on the last paragraph of page 11 and continuing to the first full paragraph on page 12 that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

35. With regards to Applicant's argument starting on the last full paragraph of page 13 and continuing to page 13, this argument is moot in light of the newly applied reference of Bartok.

36. Therefore, the rejections are proper and will stand.

Conclusion

37. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL HOBBS whose telephone number is (571)270-3724. The examiner can normally be reached on Monday-Thursday 7:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Marcheschi can be reached on (571) 272-1374. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/William H. Beisner/
Primary Examiner, Art Unit 1797

/M. H./
Examiner, Art Unit 1797